

## Editorial

# The Sources of Synthetic Vascular Smooth Muscle Cells Revisited

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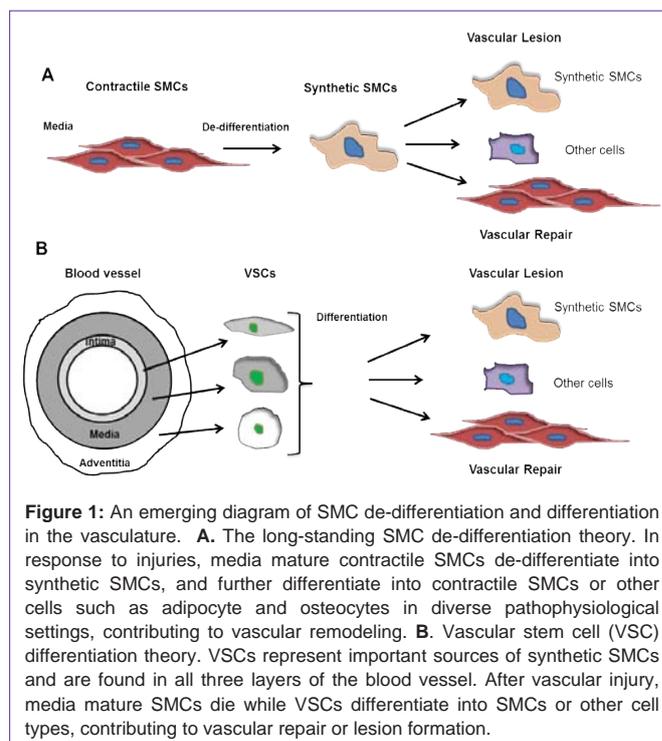
## Editorial

Vascular disease is the leading cause of mortality in the United States, and is characterized by abnormal growth of Vascular Smooth Muscle Cells (VSMCs). Extensive studies of vascular biology have shown mature VSMCs to be quiescent and contractile in normal vasculature; however, in response to injury, another unique type of VSMCs (i.e., synthetic VSMCs) becomes apparent [1]. These cells expand in number rapidly, releasing various cytokines and growth factors, all of which results in a vascular lesion. Although they may play a critical role in lesion formation, the origin of these synthetic VSMCs has been unanswered.

For more than 50 years, a widely accepted view is that, in response to vascular injury, these proliferative and synthetic VSMCs are derived from the dedifferentiation or phenotypic modulation of mature contractile VSMCs in the tunica media [2]. Other documented sources of synthetic VSMCs include bone marrow-derived stem cells and resident vascular stem cells [3-5]. However, it is clear that the differentiation of bone marrow-derived stem cells into VSMCs is an exceedingly rare event and the contribution of bone marrow-derived cells to the cellular compartment of the vascular lesion is limited to the transient inflammatory response phase [6]. Furthermore, synthetic VSMCs in a vascular lesion are exclusively derived from within the local vessel wall [6-8]. Therefore, synthetic VSMCs are reported to be likely derived from the dedifferentiation of mature VSMCs and/or resident vascular stem cells. However, the relative contributions of mature VSMC dedifferentiation and resident Vascular Stem Cell (VSC) differentiation to the generation of synthetic VSMCs in the vasculature remain unknown.

Intriguingly, emerging evidence indicates that, upon endovascular injury, mature VSMCs at the wound site die and a small population (<10%) of media stem cells are activated, proliferate, and differentiate to intimal VSMCs, thereby contributing the vascular disease [9]. These cells, named media-derived Multipotent Vascular Stem Cells (MVSCs), were found in the media of mature blood vessels. They are Smooth Muscle-Myosin Heavy Chain (SM-MHC) negative (-), Stem Cell Antigen (Sca)-1<sup>-</sup>, neural crest cell marker Sry-box (Sox)10 positive (+), endoderm marker Sox17<sup>+</sup>, neural cell marker Neural Filament-

Medium polypeptide (NFM)<sup>+</sup>, glia cell marker S100β<sup>+</sup>, and general mesenchymal stem cell marker CD29<sup>+</sup> and CD44<sup>+</sup>. These MVSCs have multilineage potential and can spontaneously differentiate into SMC-like cells that subsequently differentiate into VSMCs. Additionally, MVSCs and MSC-like cells have a differential response to the treatment of vascular growth factors bFGF, platelet-derived growth factors-β (PDGF-β) and transforming growth factor-β1 (TGF-β1). Importantly, utilizing SM-MHC-Cre/LoxP-EGFP mice generated using both ROSA26 and β-actin promoters to drive EGFP expression, the authors showed that the majority of enzymatically isolated carotid media cells are EGFP<sup>+</sup>; however, all these cells become EGFP<sup>-</sup> after being cultured and passaged for 10 days. These results indicate that proliferative/synthetic SMCs are not derived from mature VSMCs. In addition, it is the MVSCs, rather than mature VSMCs, that are activated, proliferate, repopulate the tunica media, and constitute the cellular population of a vascular lesion after injury. While this novel “MVSC” differentiation theory has been under intense scrutiny and skepticism [2], we have observed that the primary culture of rat thoracic aortic SMCs (RASCs) is most likely a process of MVSC differentiation into SMCs (unpublished data). Of note, a very recent report also demonstrated that RASCs express MVSC biomarkers and have the potential to differentiate into adipocytes and osteoblasts [10]. Collectively, even though this “MVSC” theory still needs conditional SMC lineage tracing to determine the ultimate fate of VSMCs, it has challenged the long-standing dogma of SMC



de-differentiation in the process of vascular remodeling. These novel findings raise the question of whether vascular disease is in fact an SMC disease or a stem cell disease.

Much work remains to be done. The identity and location of MVSCs need further investigation, and the definitive identification of modulated SMC phenotypes during vascular remodeling is still enigmatic. As the debates between the MVSC and SMC de-differentiation theories (Figure 1) are going [2,11], the ambiguities regarding SMC de-differentiation, as well as SMC- or other cell type-differentiation of MVSCs or other VSCs in vascular remodeling will be clarified.

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